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Review

Current pathophysiological concepts and management of pulmonary hypertension

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ABSTRACT

Pulmonary hypertension (PH), increasingly recognized as a major health burden, remains underdiagnosed due mainly to the unspecific symptoms. Pulmonary arterial hypertension (PAH) has been extensively investigated. Pathophysiological knowledge derives mostly from experimental models. Paradoxically, common non-PAH PH forms remain largely unexplored. Drugs targeting lung vascular tonus became available during the last two decades, notwithstanding the disease progresses in many patients. The aim of this review is to summarize recent advances in epidemiology, pathophysiology and management with particular focus on associated myocardial and systemic compromise and experimental therapeutic possibilities. PAH, currently viewed as a panvasculopathy, is due to a crosstalk between endothelial and smooth muscle cells, inflammatory activation and altered subcellular pathways. Cardiac cachexia and right ventricular compromise are fundamental determinants of PH prognosis. Combined vasodilator therapy is already mainstay for refractory cases, but drugs directed at these new pathophysiological pathways may constitute a significant advance.

1. Introduction

Pulmonary hypertension (PH), is defined by mean pulmonary arterial (PA) pressure (mPAP) elevation above 25 mm Hg at rest [1]. In most cases, PH accompanies cardio-respiratory conditions and does not involve the pulmonary vasculature. However, more rarely it may present itself as pulmonary arterial hypertension (PAH), defined additionally by normal left ventricular (LV) filling pressure [2]. PAH is viewed as a vasoproliferative disease with characteristic pathological abnormalities, such as arteriolar plexiform lesions, as found in most of cases. Initial symptoms, mainly fatigue and dyspnea, are usually vague and insidious, thus most cases are diagnosed when cardiac output (CO) is already low [3]. Right ventricular (RV) failure due to PH is an important cause of death [4] whose complex pathophysiological

Abbreviations: 5-HT, 5-Hydroxytryptamin, serotonin; 5-HT_{2A}, serotonin type 2A receptor; 6MWT, 6-minute walk test; AC, adenylate cyclase; AS, atrial septostomy; BMP, bone morphogenetic protein; BMPR1, bone morphogenetic protein receptor 1; BMPR2, bone morphogenetic protein receptor 2; BNP, type B natriuretic peptide; CaL, L-type Ca^{2+}-channel; CC, cardiac cachexia; CCB, Ca^{2+}-channel blocker; CCR2, chemokine receptor 2; CCR5, chemokine receptor 5; CDK, cyclin-dependent kinase; cGMP, cyclic guanosine monophosphate; CHD, congenital heart disease; CO, cardiac output; CO–A/R, co-repressors or activators; COPD, chronic obstructive pulmonary disease; CT, computerized tomography; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; CVC, central venous catheter; CX3CR1, chemokine receptor 1; CXCR4, α-chemokine receptor; DCA, dichloroacetate; DL_{CO}, carbon monoxide diffusion; e^-, electron; ECM, extracellular matrix; EF, ejection fraction; EGFR, epidermal growth factor receptor; EPC, endothelial progenitor cells; ERA, endothelin-1 receptor antagonists; ET-1, endothelin-1; ET_A, endothelin-1 type A receptor; ETC, electron transport chain; FDA, Food and Drug Administration; fPAH, familial pulmonary arterial hypertension; GC, guanylate cyclase; G_q, protein G_q; HF, heart failure; HIF-1α, hypoxia-inducible factor-1α; HIV, human immunodeficiency virus; HLT, heart-lung transplantation; Id, inhibitor of DNA binding proteins; IL-6, Interleukin-6; IP, prostaglandin receptor; IP_3, inositol 3-phosphate; iPAH, idiopathic pulmonary arterial hypertension; *iv*, intravenous; Kv1.5, O_2-sensitive K^+-channels; LHD, left-heart disease; LV, left ventricular; LT, lung transplantation; MCP-1, monocyte chemotactic protein-1; MLC, myosin light-chain; MLCK (−P), myosin light-chain kinase, and respective phosphorylated form; MMP, matrix metalloproteinases; mPAP, mean pulmonary artery pressure; NFAT, nuclear factor of activated T lymphocytes; NIH, National Institutes of Health; NO, nitric oxide; NRCT, non-randomized clinical trial; O_2^-, superoxide anion; PA, pulmonary arterial; PAP, pulmonary artery pressure; PAH, pulmonary arterial hypertension; PASMC, pulmonary artery smooth muscle cell; PCH, pulmonary capillary haemangiomatosis; PCWP, pulmonary capillary wedge pressure; PEA, pulmonary endarterectomy; PDE, phosphodiesterases; PDE_5, type 5 phosphodiesterase; PDEi, phosphodiesterase inhibitors; PDGF, platelet derived growth factor; PDGFR, platelet derived growth factor receptor; PDH (−P), pyruvate dehydrogenase, and respective phosphorylated form; PDK, pyruvate dehydrogenase kinase; PGI_2, prostacyclin; PH, pulmonary hypertension; PKA, protein-kinase A; PKG, protein-kinase G; PPH, portopulmonary hypertension; PTE, pulmonary thromboembolism; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; QOL, quality of life; RANTES, regulated upon activation, normal T expressed and secreted; RCT, randomized clinical trials; RHC, right-heart catheterisation; ROS, reactive oxygen species; RV, right ventricular; RVAD, right ventricular assist device; *sc*, subcutaneous; SDF-1, stromal cell-derived factor-1; SLE, systemic lupus erythematosus; SOD, superoxyde dismutase; SPAP, systolic pulmonary artery pressure; SR, sarcoendoplasmic reticulum; TGF-β, transforming growth factor -β; TGF-βR, transforming growth factor -β receptor; TP, ThromboxaneA_2 receptor; TnC, tenascin C; TNF-α, tumor necrosis factor-α; trp, transient receptor potential; TTCW, time to clinical worsening; TxA_2, thromboxane A_2; VEGF, vascular endothelial growth factor; VEGR, vascular endothelial growth factor receptor; WHO, World Health Organization.

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Table 1
New classification for pulmonary hypertension (PH) from the 4th World Symposium on PH (Dana Point, 2008).

Pulmonary arterial hypertension (PAH)	Non-PAH pulmonary hypertension (PH)	
	Well defined cause	Unclear or multifactorial
PAH (1)	*Left-heart disease (2)*	*Unclear/multifactorial mechanisms (5)*
Idiopathic	Systolic dysfunction	Haematologic disorders
Hereditary	Diastolic dysfunction	*Myeloproliferative disorders, etc.*
Drug/toxin induced	Valvular disease	Systemic disorders
Disease associated	*Lung diseases/hypoxia (3)*	*Vasculitis, sarcoidosis, neurofibromatosis, etc.*
CTD	COPD	Metabolic disorders
HIV infection	Interstitial lung disease	*Glycogen storage disease, thyroid disorders, etc.*
Portal hypertension	Sleep-disordered breathing	Congenital heart disease
Systemic-pulmonary shunts	Chronic exposure to high altitude	(Other than systemic-pulmonary shunt)
Schistosomiasis	Broncho pulmonary dysplasia	Other
Chronic haemolytic anaemia	Developmental abnormalities	*Fibrosing mediastinitis, chronic renal failure on dialysis, etc.*
Subclass of PAH (1′)	*CTEPH (4)*	
PVOD and PCH		

Classes are presented between parentheses. CTD, connective tissue disease; HIV, human immunodeficiency virus; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary angiomatosis; COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic PH.

mechanisms are just beginning to be understood. The last decades have been prolific in experimental and clinical studies in both PAH and PH. Several new drugs have become available [3]. Nevertheless, the prognosis remains poor, and many patients require transplantation [5]. The present review aims to summarize the most recent concepts on the epidemiology, pathophysiology, diagnosis and management of PH [6,7].

2. Aetiology and classification

Several conferences on PH have been fostered by the World Health Organization (WHO). A classification was proposed in 1973 and then modified at Evian in 1988 to better reproduce pathophysiology and clinical presentation. At Venice in 2003, the term primary PH was substituted for idiopathic PAH (iPAH) and pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) were grouped under a single PAH subcategory. In 2008, the 4th World Symposium held in Dana Point (Table 1) endorsed the expression "non-PAH PH" to address categories other than PAH. Additionally, left-heart disease PH was subdivided in systolic heart failure (HF), diastolic HF and valvular heart disease, and schistosomiasis was included as a new class of disease-associated PAH.

3. Diagnosis

During the 4th Conference (Table 2) exercise values were excluded as a criteria for diagnosis since the increase in mPAP during exercise frequently exceeds 30 mm Hg among the elderly [8]. Additionally, non-invasive echocardiographic criteria of systolic tricuspid regurgitant velocity were contemplated [9]. Nevertheless, transpulmonary flow and pulmonary venous pressure are not reliably measured by echocardiography thus right-heart catheterisation (RHC) remains the gold standard while echocardiography is usually a screening exam. RHC is mandatory in every patient, allowing the selection of patients that may benefit from Ca^{2+}-channel blockers (CCB), the positive responders during vasoreactivity test, those in whom mPAP drops more than 10 mm Hg or to values bellow 40 mm Hg with normal or increased CO, after administration of a short-acting vasodilator, such as nitric oxide (NO) [10], epoprostenol or adenosine [7].

Table 2
New diagnostic criteria for pulmonary hypertension (PH) from the 4th World Symposium on PH (Dana Point, 2008).

Method	Normal	Borderline	Clear
mPAP (mm Hg)	<21	21–25	>25
systolic tricuspid regurgitation ($m.s^{-1}$)	<2.5	2.5–2.8	>2.8

mPAP, mean pulmonary artery pressure.

4. Epidemiology

The incidence and prevalence of PAH were estimated to be 2.4–7.6 cases/million/year and 15–26 cases/million, respectively, in large population studies [11,12]. Worldwide prevalence is hard to appraise, but it is surely underdiagnosed [13] and its onus is likely greater than recognized, given the newly revealed associations with haemodialysis [14], the metabolic syndrome [15], and developing world diseases, such as human immunodeficiency virus (HIV) infection, schistosomiasis, and sickle cell disease [16]. Apart from iPAH no precise estimates of incidence or prevalence are available. Nevertheless, non-PAH PH is increasingly recognized as a major health burden. HF is the most common cause of pulmonary hypertension (PH). Not only up to 60% of patients with severe LV systolic dysfunction but also 70% of those with HF and normal ejection fraction (EF) [17] develop PH [18,19]. Moreover, PH afflicts 70% of patients with rheumatic heart disease [20]. Many patients develop chronic thromboembolic PH (CTEPH) after pulmonary thromboembolism (PTE) [20] or PH during the progression of chronic obstructive pulmonary disease (COPD). Prevalence ranges from 35 to 90% according to stage [21,22]. Systolic PAP (SPAP) is mostly limited to values ranging from 25 to 35 mm Hg, and severe PH is uncommon in advanced COPD [23]. Nevertheless, some patients develop disproportionate PH. These warrant particular attention [21], but even modest PH has a strong impact on quality of life (QOL) and survival [22]. Right HF, its most severe complication, is responsible for 10–30% of admissions due to decompensated HF [24]. Presently COPD is already responsible for 84% of *cor pulmonale* cases and, due to smoking, will be the 3 rd cause of death by 2020 [23]. Portopulmonary hypertension (PPH) is a pulmonary-hepatic vascular disorder that afflicts approximately 5–6% of patients referred for liver transplantation due to advanced liver disease. It is an underrecognized complication that adversely affects survival, after liver transplantation but presumably also in the early stages of liver disease [32,33].

5. Clinical presentation and workup

Severe disease may present with chest pain, palpitation, oedema, ascites, and syncope [9] but earlier treatment, at reversible stages, is fundamental. Diagnosis is challenging, a delay of 2 to 3 years is common and a high suspicion level is needed [13]. The clinician may find RV hypertrophy on the electrocardiogram and hilar PA prominence on the chest X-ray. Echocardiography, generally undertaken after a suspicion, may show increased SPAP, estimated by the velocity of tricuspid

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regurgitation jet, and/or increased RV outflow tract acceleration time. It is fundamental to evaluate valve or primary myocardial disease, as well as the degree of RV hypertrophy and dysfunction [9]. Comprehensive echocardiographic evaluations of RV function have been proposed as useful approaches to risk stratification in PAH [25], although magnetic resonance imaging techniques have also been used [26]. Regarding differential diagnosis, patients with suspicion of PTE should undergo the highly sensitive ventilation-perfusion (V-Q) scan. Staging and operability also relies on chest computerized tomography (CT) and angiography. High-resolution CT is useful to assess PVOD or PCH and to diagnose interstitial lung or connective tissue disease (CTD) [7,9]. Finally antinuclear antibodies, autoimmune disease markers, HIV and viral hepatitis screening, coagulation disorder markers (eg, protein S and C, lupus anticoagulants, von Willebrand factor) and type B natriuretic peptide (BNP) may be carried out for differential diagnosis [7,9]. The key feature differentiating PH resulting from left-heart disease (LHD) is elevated pulmonary capillary wedge pressure (PCWP), which is absent in PAH [27]. To establish the diagnosis of PPH patients must present with portal hypertension and not only haemodynamic criteria for PH, in the absence of other causes, but also increased pulmonary vascular resistance (PVR) [28]. Functional respiratory evaluation relies on spirometry and carbon monoxide diffusion (DL_{CO}). Spirometry may be markedly altered in lung disease, whereas minor changes are found in iPAH. DL_{CO} impairment correlates with lung vascular surface area and PAH severity [29]. The 6-minute walk test (6MWT), a common clinical trial end-point that evaluates moderate to severe heart or lung disease, is an easily performable and reproducible test originally developed as a surrogate of peak O_2 consumption (Table 3). It correlates well with CO, PVR, O_2 consumption, QOL, and predicts mortality in PAH [30]. Nevertheless, since it depends on many individual variables, it is not a reliable marker of disease progression [7]. Additionally, its validity has been questioned for CTD [31]. Cardiopulmonary exercise testing, regarded by most as gold-standard in exercise capacity evaluation and still a cornerstone in PAH functional evaluation, also assesses PH prognosis [32], but requires an experienced laboratory [33,34].

Table 3
The 6-minute walk test (6MWT) in pulmonary hypertension (PH).

Features
Submaximal exercise test
Correlates well with activities of daily living (useful for moderately severe functional impairment)
Non-specific (evaluates the response of all systems)
Well tolerated (nevertheless, appropriate response to an emergency should be available)
Measurements
Dyspnoea and fatigue self-rating at the beginning and end (according to the Borg scale, see legend)
Distance walked
Demographic and anthropometric determinants
Gender, age and ethnicity
Height and weight
Advantages
Practical and inexpensive to perform (no equipment or specially trained technicians needed)
Reproducible (estimated coefficient of variability of 8%)
Ongoing monitoring of cardiopulmonary disease progression
Evaluation of response to therapy
Limitations
Merely a rough estimate of the general functional status (does not discard specific assessment tools)
Lack of validation for connective tissue disease associated PAH (musculoskeletal involvement)
"Ceiling effect" for patients with better baseline capacity
Biases: disturbed cognition, motivational factors, test repetition, musculoskeletal limitations, etc.

A comprehensive perspective on the 6MWT including indications, contraindications, safety precautions, technical aspects, biases, can be found in the guidelines from the American Thoracic Society [134]. The 6MWT measures the distance that a patient can walk on a flat surface in a period of 6 min, patients are allowed to stop and rest. The normal walked distance for healthy 60 year-old men and women of average constitution is approximately 630 and 550 m, respectively [135], whereas idiopathic PAH patients on World Health Organization functional class IV usually walk less than 200 m [30]. A clinically important improvement in walking distance for the PAH patient is generally 44–76 m [103].
Borg scale: (0) nothing at all, (0.5) just noticeable, (1) very slight, (2) slight, (3) moderate, (4) somewhat severe, (5) severe, (7) very severe, and, finally, (10) maximal [136].

6. Pathophysiology

Although no animal model completely recapitulates human PAH, combining multiple insults, according to the multiple-hit hypothesis, yielded severe phenotypes that closely mimic it [35]. Pathophysiological knowledge, derived mostly from these animal studies, once viewed PH as an imbalance between pulmonary vasoconstrictors and vasodilators [36]. While prostacyclin (PGI_2) and NO normally govern vascular tone, endothelin-1 (ET-1), thromboxane A_2 (TxA_2) and serotonin (5-HT) take over in PH. Not surprisingly, lung arteries vasodilators have been the mainstay of therapy (Fig. 1) [3]. Nevertheless, recent research showed this view to be highly incomplete.

6.1. PAH as panvasculopathy

PAH is currently viewed as a panvasculopathy, accompanied by histological features as intimal hyperplasia, medial hypertrophy, and arteriolar occlusion by thrombosis, infiltration by inflammatory cells or angioproliferative plexiform lesions (Fig. 1) [7]. Apoptosis may generate apoptosis-resistant endothelial cell phenotypes that cross-talk with PA smooth muscle cell (PASMC) through growth factors such as transforming growth factor-β (TGF-β), that are involved in endothelial cell and fibroblast transdifferentiation and PASMC proliferation [37]. Metalloproteinase activation leads to the disruption of the basement membrane enabling inflammatory cell recruitment and further generation of mitogenic peptides [38]. The main mechanisms involved in inflammation, endothelial progenitor cell (EPC) recruitment, growth factor activity and extracellular matrix remodeling are summarized in Fig. 1. PAH shares a mitochondrial-metabolic abnormality with cancer, the "Warburg phenotype", a shift from oxidative phosphorylation to glycolysis (despite adequate O_2 supply) that enhances proliferation and prevents apoptosis (Fig. 2). Hyperpolarization of the mitochondrial membrane, reduced production of reactive oxygen species (ROS), normoxic-activation of hypoxia inducible factor-1α, overexpression of pyruvate dehydrogenase kinase (PDK) and decreased expression of O_2-sensitive K^+ channels (Kv1.5) have been postulated to underlie changes in mitochondrial O_2 sensing [39]. PDK activation suppresses aerobic glucose metabolism and decreased Kv1.5 conductance depolarizes the membrane. Dichloroacetate (DCA), a mitochondrial PDK inhibitor and Kv1.5 channel opener, improved PAH [39] both by activating pyruvate dehydrogenase (PDH) and aerobic metabolism and by restoring membrane potential and ROS production [40].

6.2. Genetics of PAH

Mutations in bone morphogenetic protein (BMP) receptor-2 (BMPR2), a constitutively active receptor responsive to TGF-β superfamily (including BMP), are seen in more than 80% of familial PAH (fPAH) cases, leading to loss of smad signalling (Fig. 3) and therefore to increased proliferation and decreased differentiation of PASMC [41,42]. Still, penetrance is low and the mutation is seen only in 10 to 20% of non-fPAH [43]. Other genetic mechanisms predispose to PAH, namely single-nucleotide polymorphisms of Kv1.5 [18], transient receptor potential (trp) channels [13], and serotonin transporters [44]. Trp channels regulate contractility and cell proliferation by intracellular Ca^{2+} [45]. Elevated 5-HT levels and 5-HT transport have been implicated in PAH pathogenesis [44].

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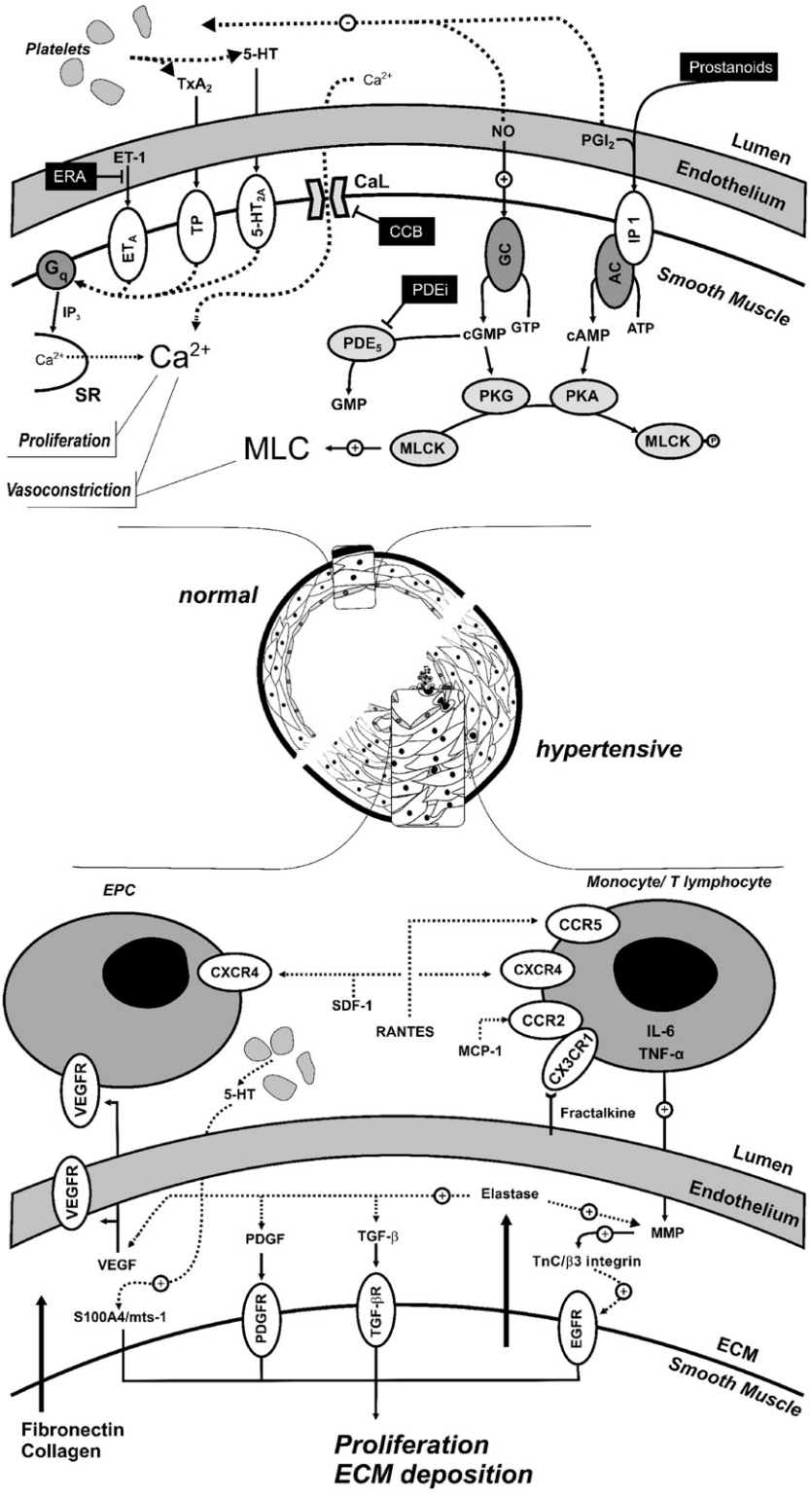

Fig. 1. Pulmonary artery smooth muscle cell (PASMC) constriction and proliferation mechanisms. The major sites of action of lung vasodilator drug classes are shown in the upper panel, namely Ca^{2+}-channel blockers (CCB), endothelin-1 (ET-1) receptor antagonists (ERA), phosphodiesterase inhibitors (PDEi) and prostanoids. Myosin light-chain (MLC) kinase (MLCK) is inactivated upon phosphorylation (MLCK-P). Other mechanisms are presented in the lower panel. Several cytokines, beyond interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), mostly produced by fibroblasts, such as stromal cell-derived factor-1 (SDF-1), monocyte chemotactic protein-1 (MCP-1), fractalkine, RANTES (regulated upon activation, normal T expressed and secreted), and vascular endothelial growth factor (VEGF) are upregulated and induce PASMC proliferation and monocyte recruitment, while monocytes upregulate the α-chemokine receptor (CXCR4) and chemokine receptors 1, 2 and 5 (CX3CR1, CCR2 and CCR5, respectively) [46]. Elastase, early activated in PH, triggers growth factors release from the extracellular matrix (ECM) and induces tenascin C (TnC) through the activation of matrix metalloproteinases (MMP). When TnC binds surface integrins on PASMCs cell-survival signals are generated and growth factor receptors are further activated. Serotonin (5-HT) induces proliferation of PASMCs by stimulation of S100A4/Mts1, a S100 Ca^{2+}-binding protein family member with metastasis-inducing ability [3]. Endothelial progenitor cells (EPC) may participate in vessel repair, but on the other hand also take part in plexiform lesions [146]. Other abbreviations: TxA_2, thromboxane A_2; G_q, protein G_q; IP_3, inositol 3-phosphate; SR, sarcoendoplasmic reticulum; ET_A, ET-1 type A receptor; TP, TxA_2 receptor; $5\text{-}HT_{2A}$, 5-HT type 2A receptor; CaL, Type L Ca^{2+}-channel; GC, guanylate cyclase; AC, adenylate cyclase; IP, prostacyclin receptor; PDE_5, phosphodiesterase type 5; PKG, protein-kinase G; PKA, protein-kinase A; VEGFR, VEGF receptor; PDGF, platelet derived growth factor; TGF-β, transforming growth factor-β; PDGFR, PDGF receptor; TGFβR, TGF-β receptor; EGFR, epidermal growth factor receptor.

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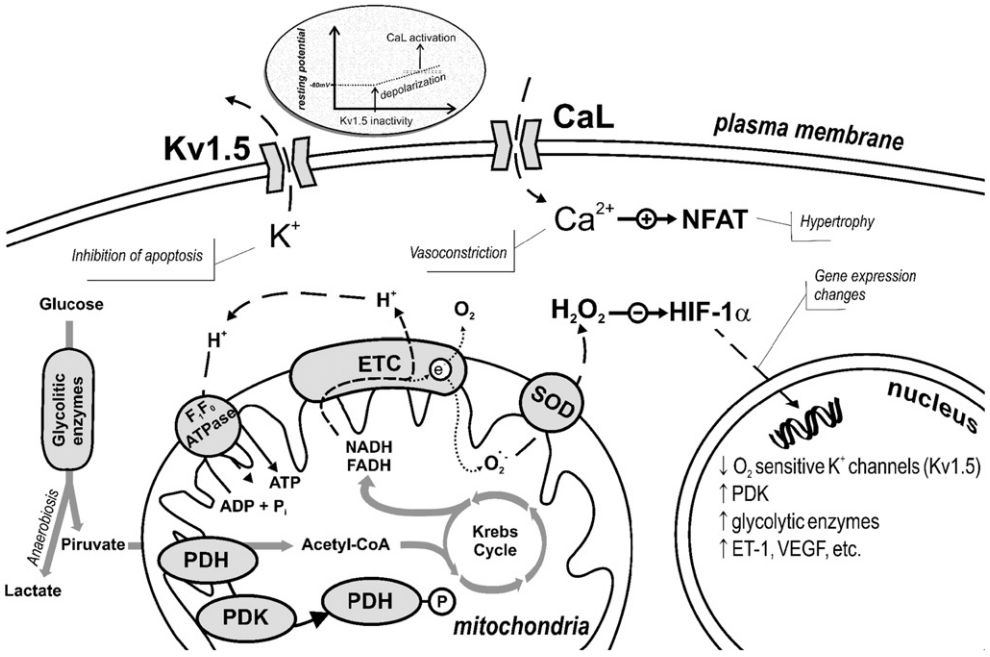

Fig. 2. Reactive oxygen species (ROS), disturbed O_2 sensing, and mitochondrial dysfunction in pulmonary arterial hypertension (PAH). During oxidative phosphorylation, electrons (e^-) are conveyed by the electron transport chain (ETC) from donors (NADH and FAH) to O_2, but minor side reactions also generate by-products, as superoxide anion (O_2^-) that must be detoxified to H_2O_2 by superoxyde dismutase (SOD) [147]. Under normoxia H_2O_2 constitutively opens plasma membrane O_2-sensitive K^+-channels (Kv1.5) and inhibits hypoxia-inducible factor-1α (HIF-1α) activity, whereas during hypoxic vasoconstriction, ROS and H_2O_2 production are decreased, Kv1.5 channels close, the plasma membrane depolarizes, Ca^{2+} enters the cell and myocytes contract. In PAH, mitochondrial abnormalities, most notably pyruvate dehydrogenase kinase (PDK) activation, shift metabolism toward anaerobic glycolysis and impair the ETC. Reduced ROS production, nuclear translocation of HIF-1α, and decreased expression of Kv1.5 ultimately lead to sustained membrane depolarization, L-type Ca^{2+}-channel (CaL) activation and hypertrophy by Ca^{2+}-calcineurin-dependent activation of the nuclear factor of activated T lymphocytes (NFAT) [146]. PDH, pyruvate dehydrogenase, and respective phosphorylated form (−P); ET-1, endothelin-1; VEGF, vascular endothelial growth factor.

6.3. Inflammation

The inflammatory state of the vessel wall has recently gained interest as primary event, rather than mere consequence of the disease [46]. Autoantibodies and infiltration by inflammatory cells are common in PAH associated with CTD but are also seen in iPAH [46]. Increased levels of cytokines and their receptors have been demonstrated, particularly in iPAH patients [47], who also present heightened expression of inflammatory cell-associated nuclear factor of activated T lymphocytes (NFAT) [48]. Cytokines involved in the pathogenesis of chronic inflammatory diseases and cancer, such as tumor necrosis factor-α (TNF-α) and IL-6, may play a role in PAH vasculopathy [49]. Our group has tested an anti-inflammatory approach in experimental models of PH with variable success [50,51]. Inflammatory activation may also underlie systemic manifestations, for instance cardiac cachexia (CC). CC is characterized not only by neuroendocrine and inflammatory activation but also by suppressed appetite and nutritional derangements [52] and poses a significant prognostic burden on HF patients [53]. CC accompanies the progression of PH, indeed, patients with severe PH have exaggerated and early post-prandial satiety hormone response [54].

6.4. The RV in PH

The RV effectively serves as a thin, compliant reservoir for blood returning to the LV whose primary function of is to deliver deoxygenated blood to the lungs, while maintaining low-pressure perfusion [55]. It is thus best suited for volume work and unable to suddenly withstand high PAP. Sudden afterload decreases stroke volume and dilates the RV [56], whereas progressive overload allows gradual hypertrophy, remodeling and substantial increases in mPAP. Curiously, although RV response partly determines the outcome [26,57], despite the fact that the RV was shown to be an independent therapeutic target in experimental PH [58], and even though RV remodeling is potentially reversible, as seen after lung transplantation (LT) [59], little is known about the mechanisms underlying RV dysfunction [55]. Many have shown neuroendocrine activation can contribute to RV hypertrophy [60,61], fibrosis and apoptosis, as well as to oxidative stress, and activation of inflammatory cytokines and growth factors [55,62]. A state of myocardial hibernation has been proposed based on systolic flow impediment to coronary arteries which is proportional to RV pressure and mass [63]. In contrast to the normal flexible metabolism, in RV hypertrophy the myocardium relies solely on anaerobic glucose metabolism partly due to PDK activation [64] and possibly impaired mitochondrial energy-producing ability [65]. Moreover, changes in cardiomyocyte redox state can underlie electrophysiological instability and remodeling, by mechanisms similar to those already described for pulmonary vessels [66]. Experimental findings and clinical observations suggest that elevated mPAP cannot be the single driver for RV failure [62], therefore, targeting the RV may be a promising approach [6]. As for the LV myocardium, echocardiography shows compromised LV function in various aetiologies of PH [67], mainly due to ventricular interdependence and impaired filling [68]. Nevertheless, myocardial abnormalities partly underlie LV dysfunction. Indeed, despite immediate restoration of LV geometry and RV function, LV filling is only normalized 1 year after single-LT in severe PH [69], and combined heart-lung transplantation (HLT) is favored if LV function is impaired because the LV may not recover after LT alone [70]. We have confirmed intrinsic LV myocardial dysfunction and neuroendocrine activation experimentally [61,71].

6.5. Pathophysiology of non-PAH PH

Contrarily to PAH, and paradoxically, few data are available on the pathophysiology of the far more common non-PAH PH. Regarding chronic pulmonary disease, several mechanisms are potentially responsible. Hypoxia, such as is found at high altitude, is known to

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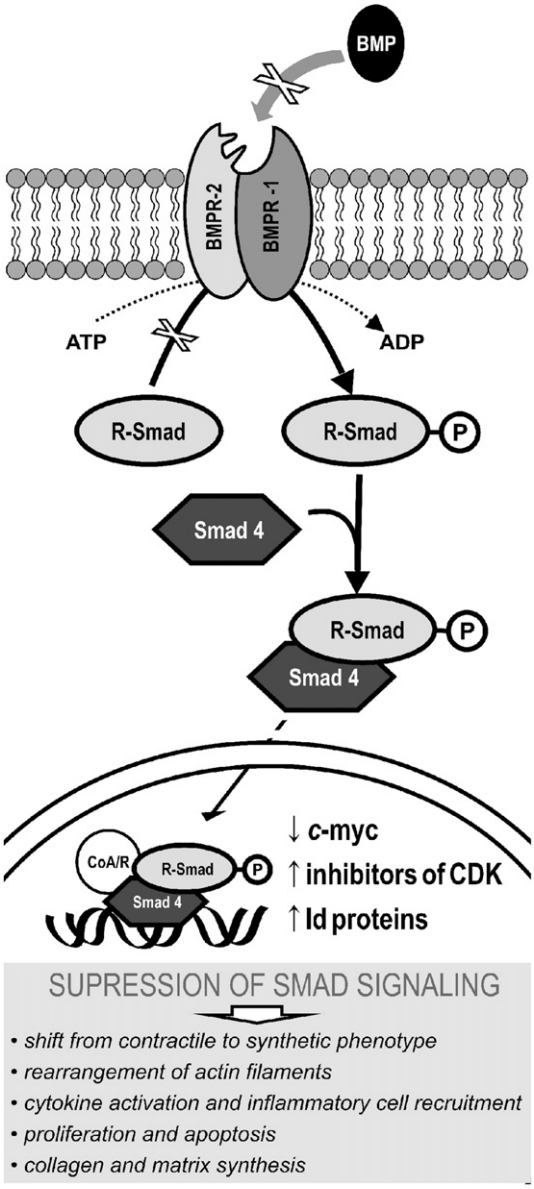

Fig. 3. Growth-promoting pathways in bone morphogenetic protein (BMP) receptor type 2 (BMPR-2) mutations. Bone morphogenetic protein (BMP) receptor type 1 (BMPR-1) and -2 dimerize upon activation by BMP and initiate a cytosolic receptor-activated Smad protein-signaling cascade. Smads (homology with drosophila's mothers against decapentaplegic – MAD – and Caenorhabditis elegans' small phenotype – sma – proteins) ultimately complex with common partner Smad4 and translocate to the nucleus. The weak Smad–DNA interaction requires co-repressors or activators (Co–A/R) [148]. Signal disrupting mutations in BMPRII can be found in the ligand-binding domain, in the kinase domain or in the cytoplasmic tail. Suppression of Smad signalling partly underlies the hypertrophic and proliferative phenotype of pulmonary artery smooth muscle cells (PASMC) [149]. In normal PASMC, BMP stimulates transcriptional activation of cyclin-dependent kinase (CDK) inhibitors and repression of c-*myc*. CDK inhibitor prevents progression in cell cycle, while c-*myc* encodes a transcriptional activator responsible for growth and proliferation [150]. Inhibitor of DNA (Id) binding proteins, a family deprived of DNA-binding domain that acts by inhibition of transcription factors, are also major targets. Failure to induce Id genes makes PASMC unresponsive to the growth suppressive effects of BMPs [151]. Prostanoids, by cyclic adenosine monophosphate and a direct effect on the Id promoter, drive the expression of Id proteins [148].

induce PH, but low arterial O_2 is not an independent predictor of mPAP, therefore after the Evian Conference COPD-associated PH was no longer classified as 'associated with hypoxemia' [29]. Pulmonary vessels in COPD consistently develop intimal fibro-elastic thickening and overall muscularisation but this does also not provide a consistent explanation [72]. Endothelial dysfunction and inflammation, are currently viewed as the key to vascular remodeling [73]. Findings strongly suggest an involvement of vasoactive mediators and cytokines [72]. Plasma IL-6 correlates with mPAP and certain IL-6 genotypes are associated with PH development in COPD [74]. Indeed, vascular remodelling and endothelial dysfunction can be observed in mild COPD without hypoxaemia and in ordinary smokers [75]. Symptomatic CTEPH affects 3.8% of patients within 2 years of initial PTE [76], but up to 5.1% of patients may develop definite CTEPH [77]. Unlike PAH, CTEPH is mainly associated with obstructions in larger vessels. Its pathophysiology remains obscure, while most argue that it results from recurrent pulmonary embolism, it has also been suggested that endothelial dysfunction could lead to thrombus formation *in situ*, and, in fact many patients do not have a clear history of embolism [78]. Variable degrees of small vessel disease, a PAH-like vasculopathy, accompany CTEPH and the mechanisms that underlie them are probably common to PAH, namely endothelial dysfunction [79]. As for LHD, two major mechanisms underlie PH, an hydrostatic and a vasoreactive. Increased filling pressures are transmitted to the pulmonary circulation and generate, initially, pulmonary venous hypertension, but, later on, also PVR increase. SPAP correlates tightly and is roughly twice the PCWP [80]. When the compensatory mechanisms of the highly distensible pulmonary vasculature are surpassed PA pressure increases first on exertion and later on also at rest. Endothelial dysfunction, sympathetic-adrenergic stimulation and disturbances of 5-HT, TxA_2 and angiotensin-II production further aggravate PH [81], contributing to structural changes at the capillary level, namely swelling of the endothelial cells, thickening of the basal lamina, and proliferation of reticular and elastic fibrils. These changes participate in increasing PVR, decreasing permeability of the vascular bed, and lower the possibility of developing pulmonary edema, but ultimately lead to increased likelihood of right ventricular failure [82]. These changes are initially reversible if cardiac filling pressures are reduced, but on the long term become irreversible and pose a relative contraindication to cardiac transplantation [83].

6.6. Prognosis

Although PAH has been most extensively studied, its rarity, diverse etiology and changing therapeutics preclude an estimation of yearly mortality rates. An early registry followed 194 patients with iPAH from 1981 to 1985 and estimated a median survival of 2.8 years, with 1-, 3-, and 5-year survival rates of 68, 48, and 34%, respectively [84]. Present-day registries, however, reveal a better prognosis, with 1 year survival ranging 83 to 88% and 3 year survival 58 to 72% [85]. A risk-prediction equation could be derived from multivariate analysis, including gender, 6MWT, and CO at diagnosis as covariates [86]. Four variables were associated with increased 1-year survival: WHO functional class I, 6MWT $\geq$ 440 m, BNP $<$ 50 pg/mL, and $DL_{CO} \geq 80\%$ of predicted [86]. Recently, echocardiographic evaluation of RV function has also been successfully used for risk stratification in PAH [25]. The progression in non-PAH PH is generally slower and the overall prognosis is better. Still, there is a substantial impact on QOL and survival [22,27]. The level of PAP is a good indicator of prognosis in COPD and a 50% 5-year survival rate has been reported with PH [87]. Regarding CTEPH, survival changed dramatically. Before the advent of pulmonary endarterectomy (PEA) patients who had mPAP higher than 30 mm Hg steadily progressed to PH and 2 year-survival was lower than 20% after it reached 50 mm Hg [88]. Currently, in experienced centres and carefully selected patients, PEA provides remarkable haemodynamic and clinical improvement with low procedural mortality rate [5]. In severe HF, the EF of the RV is the most important determinant of short-term prognosis among hemodynamic variables [89]. Although increased mPAP is frequently coupled with reduced RV function, exceptions must be taken in account during prognostic stratification [19].

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Table 4
Summary of randomized clinical trials (RCT) on pulmonary arterial hypertension (PAH).

Class	Drug	Year	Author	Study type	Sample	Patients	Follow-up	Positive outcomes
Prostanoid	Epoprostenol	1996	Barst [96]	RCT (not blind)	iPAH (WHO III–IV)	81	12 weeks	Haemodynamics, QOL, WHO class, survival
	Treprostinil (sc)	2002	Simmoneau [98]	RCT	iPAH, CTD and CHD (WHO II-IV)	470	12 weeks	Haemodynamics, 6MWT, clinical evaluation
	Iloprost (inh)	2002	Olschewski [99] (AIR)	RCT	iPAH, CTD and CTEPH (WHO III-IV)	203	12 weeks	Haemodynamics, 6MWT, QOL, WHO class
	Beraprost	2002	Galiè [137] (ALPHABET)	RCT	iPAH, CTD, CHD, portal hypertension and HIV (WHO II-III)	130	12 weeks	Exercise tolerance, 6MWT, clinical evaluation
		2003	Barst [138]	RCT	iPAH, CTD and CHD (WHO II-III)	116	1 year	Exercise tolerance, 6 MWT, TTCW,
ERA	Bosentan	2002	Rubin [103] (BREATHE1)	RCT	iPAH, CTD or SLE (WHO III-IV)	213	16–28 weeks	Exercise tolerance, 6MWT, WHO class, TTCW;
		2005	McLaughlin [139]	RCT (not blind)	iPAH (WHO III-IV)	169	3 years	Survival (NIH prediction)
		2006	Galiè [140] (BREATHE5)	RCT	CHD (WHO III)	54	16 weeks	Haemodynamics, 6 MWT
		2008	Galiè [106] (EARLY)	RCT	iPAH, CTD, CHD, HIV (WHO II)	185	6 months	Haemodynamics, NT-pro-BNP and TTCW
		2008	Jais [123] (BENEFIT)	RCT	CTEPH (WHO II–IV)	157	16 weeks	Haemodynamics
	Ambrisentan	2005	Galiè [141]	RCT (dose ranging)	iPAH, CTD, HIV and anorexigen (WHO II–III)	64	12 + 12 weeks (not-blind)	Haemodynamics, 6 MWT, clinical evaluation
		2008	Galiè [142] (ARIES 1 and 2)	RCT	iPAH, CTD, HIV and anorexigen	202 + 192 (parts 1 and 2)	12 weeks	6MWT, WHO class, QOL, TTCW, NT-pro-BNP
		2009	Oudiz [108] (ARIES 1, 2 and E)	RCT	iPAH, CTD, HIV and anorexigen	383	2 years	6MWT, TTCW and survival (combined outcome)
	Sitaxsentan	2004	Barst [143] (STRIDE1)	RCT	iPAH, CTD and CHD (WHO II–IV)	178	12 weeks	Haemodynamics, 6MWT, WHO class
		2006	Barst [144] (STRIDE2)	RCT	iPAH, CTD and CHD (WHO II–IV)	245	18 weeks	6MWT, WHO class
PDEi	Sildenafil	2005	Galiè [110] (SUPER1)	RCT	iPAH, CTD and CHD (WHO II–IV)	278	12 weeks	Haemodynamics, 6MWT, WHO class
	Tadalafil	2009	Gàlie [145] (PHIRST)	RCT (dose ranging)	iPAH, CTD, CHD, HIV and anorexigen	405	16 weeks	Haemodynamics, WHO class, 6MWT, TTCW, QOL
Combined	Bosentan + Iloprost (inh)	2006	McLaughlin [114] (STEP)	RCT	iPAH, APAH (WHO III)	67	12 weeks	Haemodynamics, WHO class, TTCW
	Epoprostenol + sildenafil	2008	Simmoneau [115] (PACES)	RCT	iPAH and CTD	267	16 weeks	Haemodynamics, exercise tolerance, QOL, TTCW
	Bosentan or sildenafil + treprostinil (inh)	2010	McLaughlin [100] (TRIUMPH I)	RCT	iPAH, CTD, HIV and anorexigen (WHO III–IV)	255	12 weeks	QOL, NT-pro-BNP

RCT on PAH therapeutics are summarized according to drug class, drug type and publication date. Study acronyms are presented when applicable. Studies enrolling less than 50 patients as well as studies involving specific PAH groups, namely HIV-related and portal hypertension-related were excluded. iPAH, idiopathic pulmonary arterial hypertension; WHO, World Health Organization; QOL, quality of life; 6MWT, 6-minute walk test; NIH, National Institute of Health; APAH, disease associated pulmonary arterial hypertension; CTD, connective tissue disease APAH; CHD, congenital heart disease APAH; CTEPH, chronic thromboembolic pulmonary hypertension; HIV, human immunodeficiency virus APAH; TTCW, time to clinical worsening; SLE, systemic lupus erythematosus APAH; NT-pro-BNP, N terminal fragment of pro-type B natriuretic peptide. Study acronyms stand for: AIR, Aerosolized Iloprost Randomized; ALPHABET, Arterial Pulmonary Hypertension and Beraprost European Study Group; BREATHE, Bosentan Randomized trial of Endothelin Antagonist THErapy Study Group; EARLY, Endothelin Antagonist tRial in miLdlY symptomatic PAH patients; BENEFiT, Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension; ARIES, Ambrisentan in pulmonary hypertension, randomized, double blinded, placebo controlled, multicenter, efficacy studies); STRIDE, Sitaxsentan To Relieve ImpaireD Exercise; SUPER, Sildenafil Use in Pulmonary Arterial Hypertension Study Group; PHIRST, Pulmonary Arterial Hypertension and Response to Tadalafil; STEP, Safety and pilot efficacy Trial in combination with bosentan for evaluation in pulmonary arterial hypertension; PACES, pulmonary Arterial hypertension Combination study of epoprostenol and sildenafil; TRIUMPH I, efficacy and tolerability of inhaled Treprostinil sodium in patients with severe pulmonary arterial hypertension.

7. Therapeutics

Treatment of PAH has evolved considerably over the past decade, many treatment algorithms have been proposed, mainly based on studies conducted in patients with iPAH and PAH associated with CTDs. In Table 4 we summarize the major therapeutic studies on PAH.

Several general measures can be recommended. Regarding exercise practice, patients may practice low level aerobic exercise, such as walking, whereas exertion that may lead to breathlessness, dizziness or chest pain should be avoided. Some patients may not tolerate high altitudes, for instance during airplane flights, and therefore require in-flight O_2 administration. It is currently recommended for patients either in WHO classes III and IV or whose arterial O_2 pressure is below 60 mm Hg. Dietary sodium restriction can be advised particularly in RV failure ($\leq 2.4\ g.d^{-1}$), but current European Society of Cardiology guidelines do not recommend it. Immunization against common respiratory pathogens is recommended [7]. PAH is a contraindication to pregnancy due to the high mortality rate [90].

Despite the lack of randomized controlled trials (RCT), the initial therapeutic, and largely supportive, approaches to the treatment of PAH were anticoagulation, diuretics, O_2 therapy and digoxin. Observational studies suggested improved survival after anticoagulation in patients with iPAH, therefore most experts recommend anticoagulation in iPAH, heritable PAH, and PAH due to use of anorexigens (titrated to international normalized ratio of 2.0–3.0). As for non-iPAH, anticoagulation may be advised for severe cases [7]. Diuretics are used to manage HF symptoms. O_2 therapy in hypoxemia is employed strictly to avoid vasoconstriction. Based on a short-term effect study, digoxin may be used in patients with low CO, but its use is clearly only recommended in patients with supraventricular tachyarrhythmias

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[91]. During the last two decades substantial RCT and pharmacological research have yielded several new and more effective alternatives to treat PH. The main pharmacological classes will be briefly presented. Most of the studies are small scaled and short-termed, not suitable for survival analysis, but a recent meta-analysis found an overall benefit in mortality [92]. Nevertheless, most therapies reduce mPAP by only 10–20%, with the exception of strong responders to CCB. Despite all the advancement, many patients still remain symptomatic, with a suboptimal QOL and warrant combined therapy or even invasive or surgical procedures.

7.1. Ca^{2+} channel blockers

A marked improvement in survival rates was shown with long-term high-dose CCB therapy for patients with iPAH and a positive vasoreactivity test [93]. Long acting nifedipine, diltiazem, or amlodipine are more commonly used. If there is no recovery to functional classes I or II patients are deemed as non-responders and should discontinue CCB. True responders are rare in non-iPAH [94]. Indiscriminate use is not recommended, due to systemic vasodilation and negative inotropic effects [95].

7.2. Prostanoids

There are presently several commercially available prostanoid formulations. Intravenous (*iv*) epoprostenol was the first shown to improve functional class, hemodynamics and survival in a 12-week follow-up period in patients with iPAH of classes III and IV [96]. These beneficial effects were reproduced in long-term observational comparisons with historical controls [97]. Moreover, epoprostenol was also evaluated in CTD associated PAH and other forms of non iPAH with favourable outcomes. Presently, because of the complex administration and cumbersome follow-up, epoprostenol use is mainly confined to highly experienced centres. Patients must keep a central venous catheter (CVC) and handle drug preparation and infusion. Dosing must be carefully titrated. Most patients do well with an initial in-hospital dose of 2 $ng.kg^{-1}.min^{-1}$ and a dose range between 25 and 40 $ng.kg^{-1}.min^{-1}$. Unfortunately, substantial side-effects have been reported, namely flushing, headache, and sudden death after abrupt discontinuation, as well as risk of infection related to CVC [7]. Treprostinil, a longer half-life prostanoid, amenable to administration by subcutaneous (*sc*) route, circumventing the need for CVC, showed minor beneficial effects in patients with functional classes II–IV of idiopathic, CTD and (CHD) associated PAH [98]. The Food and Drug Administration (FDA) approved it for functional classes II–IV also by *iv* route, when the *sc* route is not tolerated due to pain or erythema. It is currently not approved by the European Medicines Agency (EMA). On another attempt to facilitate administration, iloprost was developed for inhalation by aerosol device. After a 12-week administration, iloprost improved the 6MWT and functional class in a multicentre RCT enrolling patients with PAH of different aetiologies [99]. Treprostinil is now also available by inhalation [100], and trials of oral formulations have been iniciated (FREEDOM, Trial of Oral Treprostinil in Pulmonary Arterial Hypertension).

7.3. Endothelin receptor antagonists

We have previously reviewed the role of ET-1 and its antagonists (ERA) in cardiovascular pathophysiology [101]. Briefly, after a small magnitude RCT had shown improvement in the 6MWT, mPAP and CO with the non-selective ERA bosentan [102], a larger scale study conducted in patients with idiopathic or CTD associated PAH, reproduced these findings and reported improvement in time to clinical worsening (TTCW), a secondary endpoint defined as a composite of mortality, LT, hospitalization, discontinuation due to lack of recovery or need for epoprostenol or atrial septostomy (AS) [103]. As an important side-effect, bosentan dose-dependently altered hepatic function. Anemia can also occur and the FDA therefore recommends liver function test and haematocrit surveillance [7]. Long-term evaluation as a first-line drug in functional class III patients also revealed good results, although many patients demanded prostanoids [104]. In fact, improved survival was only demonstrated by comparison with historical data from epoprostenol treated iPAH WHO class III patients, and unfortunately the two cohorts were not comparable [105]. By now, bosentan has also been tested in CHD, HIV-associated PAH and CTEPH with favourable results. Moreover, it has been successfully used in a large sample of mildly symptomatic, class II, multiple cause-PAH patients improving haemodynamics and TTCW [106]. Sitaxentan a selective ET_A ERA initially was shown to have comparable effects to bosentan in iPAH and PAH associated with CTD or CHD, but has been withdrawn from market due to two fatal cases of liver failure [107]. Ambrisentan, another selective ET_A ERA, also improved the 6MWT and TTCW, which was reproducible in long-term studies [108]. It is approved by the FDA since 2007 and it has also been approved by the EMA for PAH patients in functional classes II and III. Indeed, it is the only ERA approved for WHO class II.

7.4. Phosphodiesterase inhibitors

Phosphodiesterases (PDE) degrade cyclic guanosine monophosphate (cGMP) therefore PDE inhibitors (PDEi) potentiate the effects of cGMP generated by NO activation of guanylate cyclase. NO and NO donors have been extensively used as a rescue therapy to mitigate mPAP in the perioperative period and in the critically ill patient, particularly in children [109]. Sildenafil, the first used PDEi, was shown to improve 6MWT, WHO functional class and mPAP in idiopathic, CTD or CHD associated PAH, but there were no differences in TTCW [110]. The FDA approved sildenafil in low doses for patients with PAH although there is some debate as to whether higher doses might confer additional benefits [111]. Other PDEi are currently under study. Tadalafil, recently approved by both FDA and the EMA, has a longer half-life than sildenafil and is amenable to once-daily dosing. Nevertheless, unlike sildenafil, due to its hepatic metabolism and renal clearance, dose adjustments are recommended for patients with renal or hepatic function impairment [112].

7.5. Combination therapy

The possibility to combine distinct drug classes that target different molecular pathways in order to improve clinical efficacy and minimize side-effects is an attractive perspective. After an initial attempt to combine bosentan and epoprostenol in a small scale and underpowered trial conducted on patients with either iPAH or PAH associated to CTD that proved unsuccessful [113], another trial that combined inhaled iloprost with bosentan in patients who remained symptomatic showed improvement in functional class, TTCW and haemodynamics [114]. More recently, the addition of sildenafil to PAH patients who remained symptomatic on a stable dose of *iv* epoprostenol improved the 6MWT, as well as mPAP, CO, and TTCW [115], while the addition of inhaled treprostinil to WHO III and IV PAH patients undergoing either bosentan or sildenafil chronic therapy showed only clinical benefits in QOL [100], and the introduction of oral treprostinil failed to achieve statistical significance in 6MWT (FREEDOM, unpublished results).

7.6. Invasive and surgical strategies in PAH

These include AS and LT or HLT. Other possibilities, such as the RV mechanical assist devices (RVAD) are still poorly investigated. AS creates a right-to-left shunt that unloads the RV, decreases mPAP, and improves LV filling. The increase in CO offsets the shunting of deoxygenated blood and ameliorates O_2 delivery. Increased CO allows bridging to transplantation in up to 40% of patients [116]. Nevertheless, it is merely palliative and procedural mortality is still high therefore it is just a last resort for patients on maximal medical therapy and inotropic support. Improved

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techniques are being currently explored to reduce procedural risk [5]. Currently, PAH is responsible for approximately 4% of LT and HLT, and although there is a substantial procedural related mortality, the long-term outcome is better than with medical therapy alone, with a 47% survival after 5 years [117]. The type of transplant is still a matter of debate and highly related to the experience of each centre. Generally HLT is preferred either when patients have intractable HF or are dependent on inotropic support or if PH is secondary to CHD or LHD [70].

7.7. Therapeutic algorithm

Management must be tailored to each patient according to disease severity, comorbid conditions, drug side-effects and each centre's experience. CCB are reserved for iPAH patients with a positive vasoreactivity test and stable hemodynamics, otherwise first line therapy should consist of ERA or PDEi, unless the oral route is not available, patients are in functional class IV or present overt RV failure. In these cases, the first choice is an *iv* prostanoid. Moreover, combination therapy should always be kept in mind, particularly when side-effects arise or patients are not responding. Enrolment in clinical trials with newer pharmacological agents may be an option but AS and transplantation should be considered before systemic deterioration. Early referral for transplantation is crucial particularly for refractory cases [7]. A simplified therapeutic algorithm is suggested in Fig. 4.

7.8. Non-PAH PH

Patients will benefit from medical optimization of their primary disease, but significant PH may persist. Some patients actually present disproportionate PH not easily attributable to the underlying condition.

In left-heart disease prostanoids, with the exception of inhaled route, are usually contraindicated due to systemic vasodilation [118]. ERA trials have been interrupted prematurely due mainly to side-effects and absence of clinical benefit, even with reduced dose [119], but selected cases may benefit from short trials as a bridge to transplantation [120]. As for PDEi short-term hemodynamic benefits, as well as long-term improvements have been documented [121].

Mild levels of PH are amenable to optimization of medical therapy in COPD. If PH is disproportionate, and other PH causes have been ruled out, many centres are routinely employing vasodilators despite V-Q mismatch [122]. CTEPH is potentially curable with PEA [5]. Yet, many patients are not candidates so they remain anticoagulated and on diuretics. Many centres are promptly using new PAH drugs off-label if there is associated vasculopathy [123].

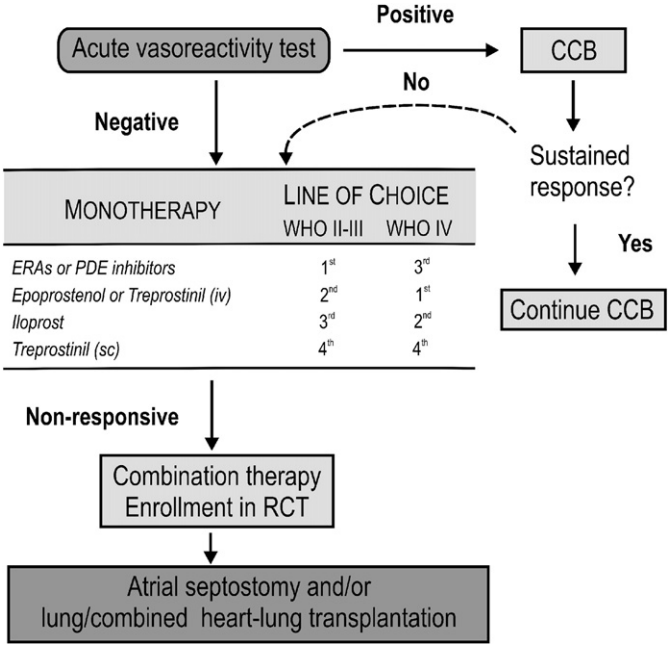

Fig. 4. Algorithm for pulmonary arterial hypertension (PAH) management. CCB, calcium channel blockers; WHO, World Health Organization; ERA, endothelin-1 receptor antagonists; PDEi, phosphodiesterase inhibitors; RCT, randomized clinical trials; *iv*, intravenous; *sc*, subcutaneous. *, among the ERAs only ambrisentan is approved for WHO class II patients.

7.9. Recent progresses and future targets in PH

Based upon the most recent experimental findings, clinical trials targeting altered metabolic and signalling pathways are warranted. DCA and Kv1.5 channel gene transfer have been successful in experimental studies [39], as well as trp channel inhibitors, growth factor receptor inhibitors and intracellular kinase inhibitors [3,124]. Inflammatory response modulation has also been a major research topic. After several animal studies demonstrating beneficial effects of statins [124], possibly due to pleiotropic effects, a human study disappointingly showed no long-lasting improvement [125]. Other immunomodulatory agents have been successful in animal experiments [50,126], but beneficial effects are mainly confined to CTD associated PAH [127]. We have also reported disturbances in endogenous endocrine and paracrine systems [128,129] that may be targeted. Another tempting possibility is the recruitment or infusion of EPC. The number and function of EPCs predicts prognosis, and most currently used drugs increase circulating EPC numbers [130]. Circulating EPCs home to sites of endothelial injury, promote revascularization and improve vascular homeostasis [131], endothelial dysfunction may be related to the lack of EPCs [130]. Finally, we must bear in mind that RV failure is the final and most severe complication of PH. Agents such as levosimendan that vasodilate lung vessels but are also positive inotropes are predictably good therapeutic tools. Still, the clinical efficacy of these drugs has only just started to be evaluated [132,133].

Conflict of interest statement

None declared.

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